



# **Current Trends in Translational Research Regarding Microdosing and Phase 1 Optimisation**

Ole J. Bjerrum  
Professor, DMSc

# Methodological Research for Drug Development I



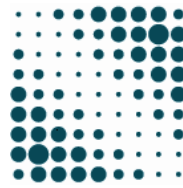
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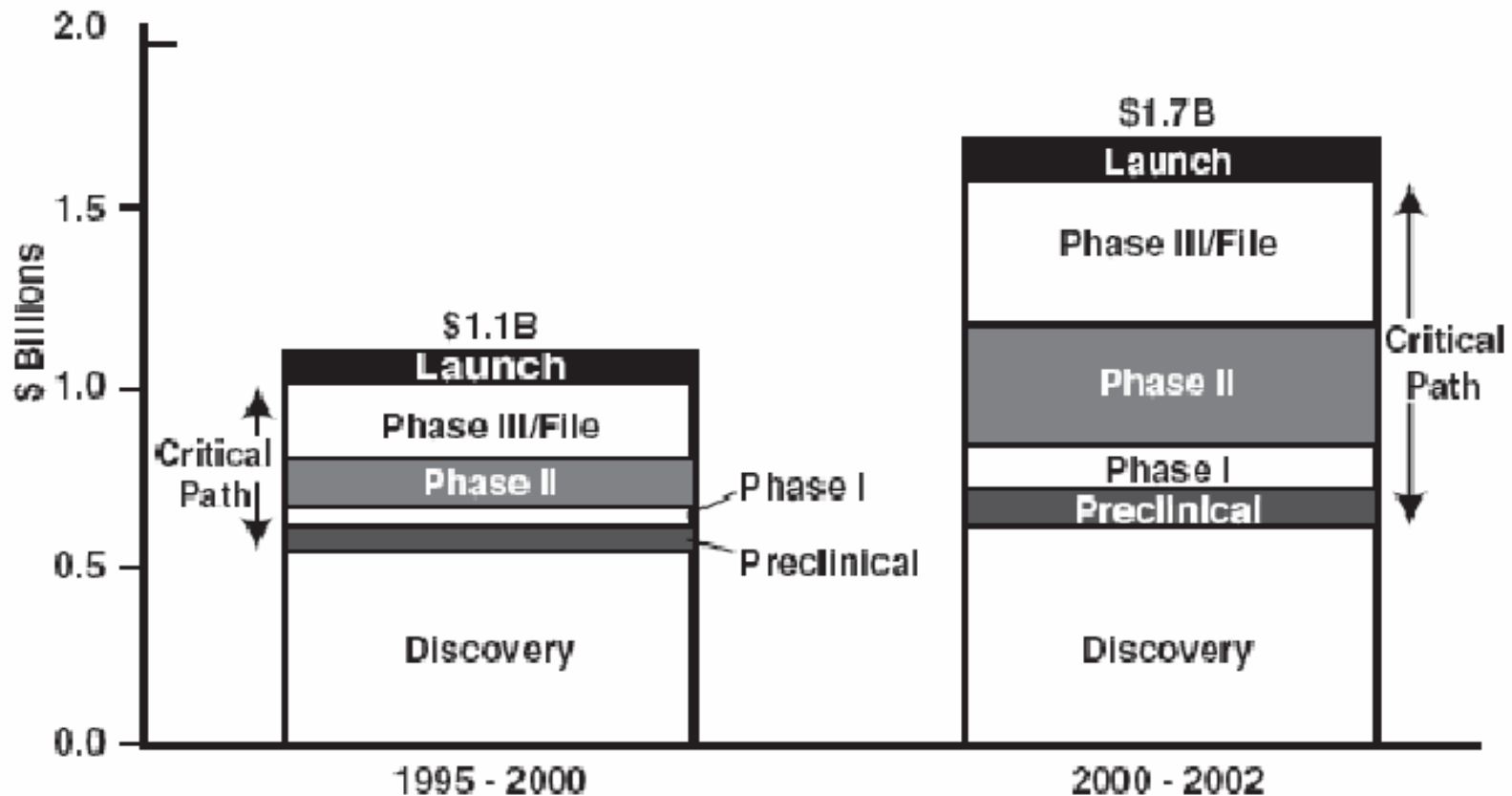
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Basic Research for discovery of new drug targets is crucial, but innovation for methodological improvements of the drug development process are equally important.

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- Academic research has an important role to play but progress is dependent on public grants.

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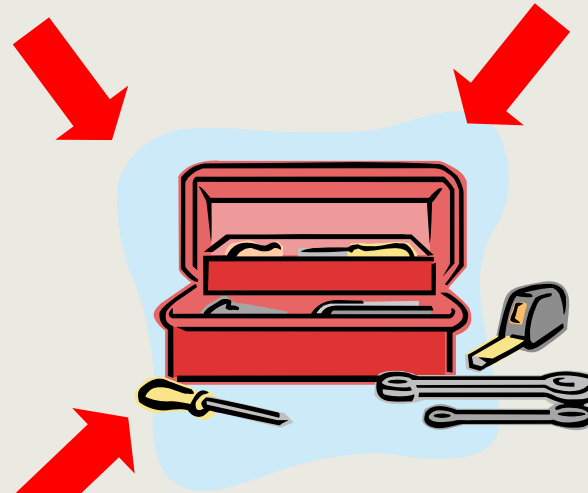
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# TOOLS FOR CANDIDATE SELECTION



PK/PD modelling

Physiological scaling methods



Preliminary animal data

*In vitro* models

**Microdosing**

# Microdosing: Concept



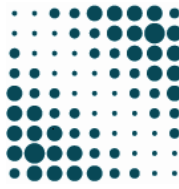
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- Assay through AMS and PET (Accelerator Mass Spectrometry and Positron Emission Tomography)



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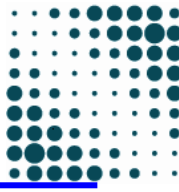
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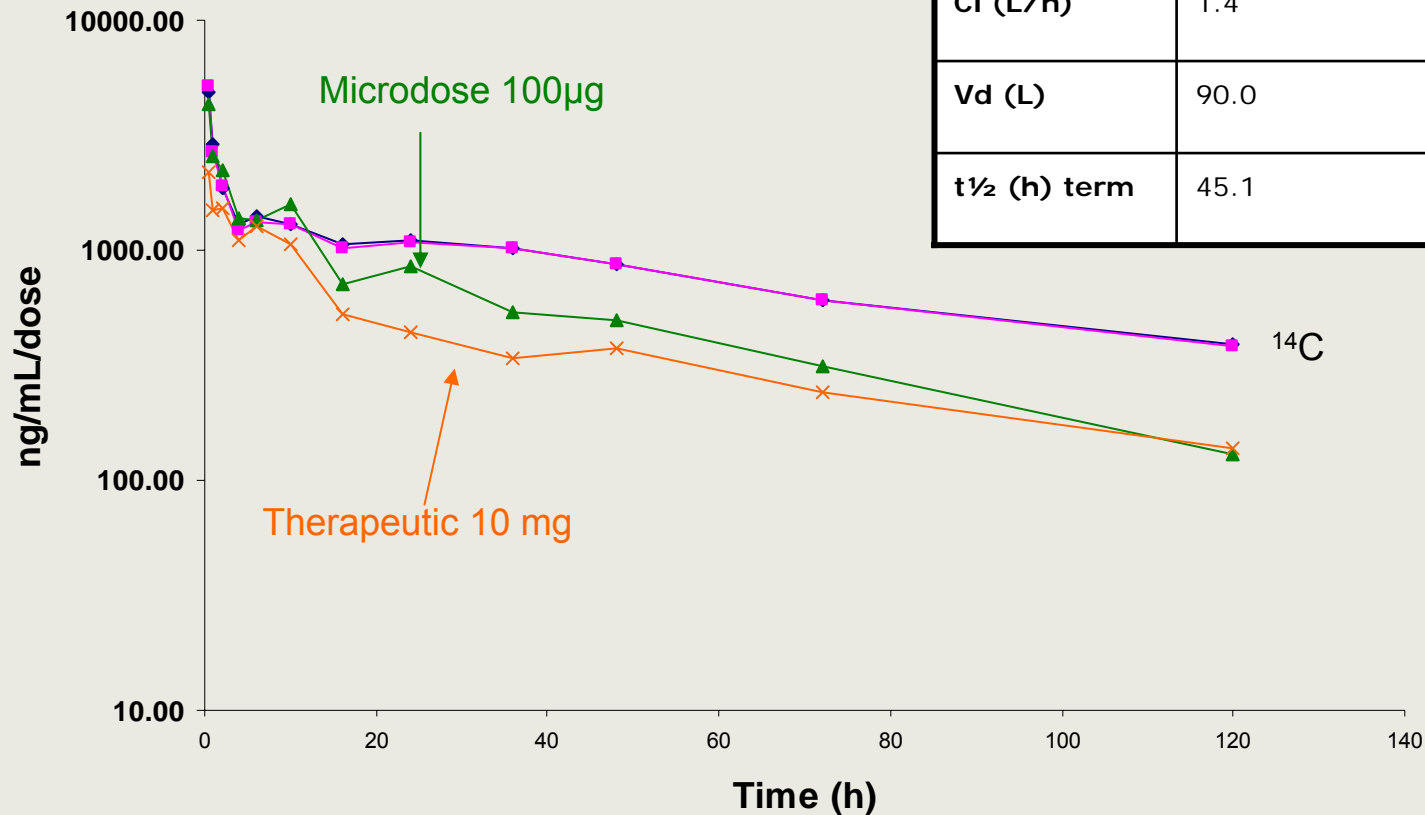


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- Using Accelerator Mass Spectrometry, a series of well characterized drugs with different ADME properties are examined with micro- and therapeutic dosing of human volunteers (N=6)

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## Diazepam (normalised for dose)



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# MICRODOSING (Phase 0) OFFERS

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- Increased speed in development (less costs)
- First in Man push forward in time (limited tox)
- Mechanistically information (PK, ADME, metabolites from Man)
- Rough indication on regional PK (organ at risk)
- Suggest starting dose for Phase I studies
- Give relations between animal species/models and Man
- Evaluate the disease model

# First Human dose trial design



## Traditional

Parallel single-dose dose escalation

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PK and safety data

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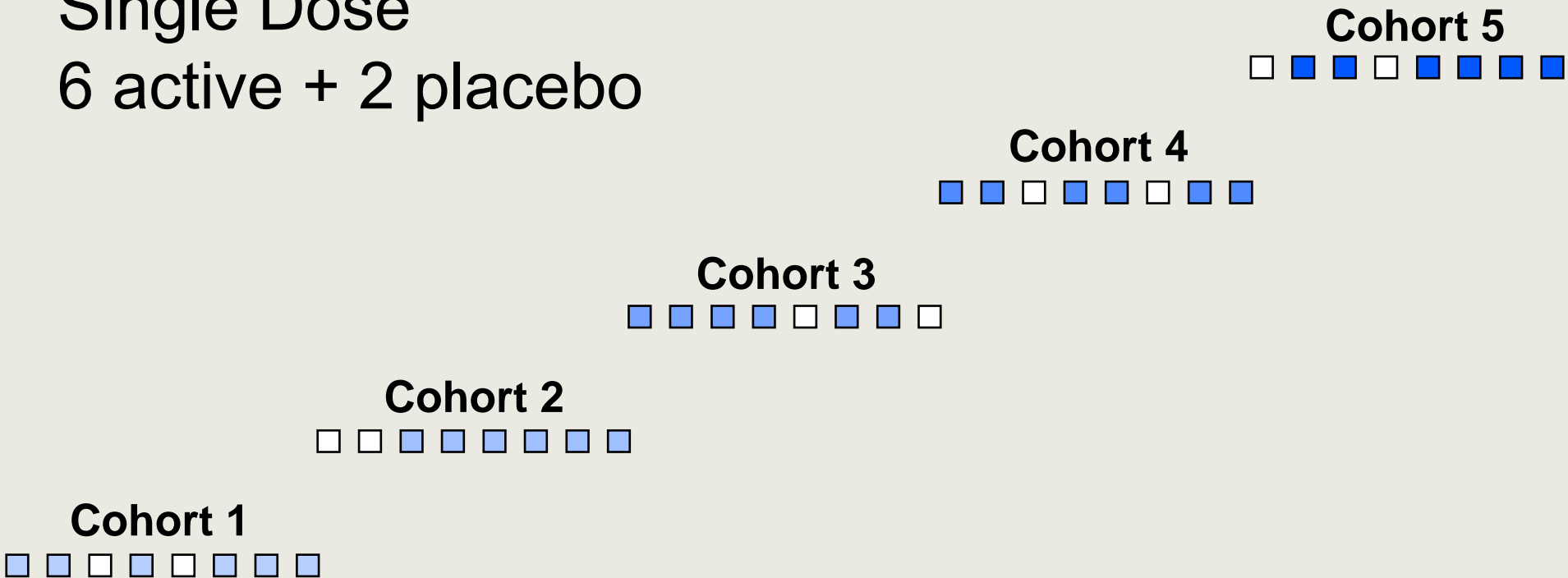
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*Both regarding design and cohort size to allow more information to be collected at more suitable dose levels, using fewer subjects and less time.*

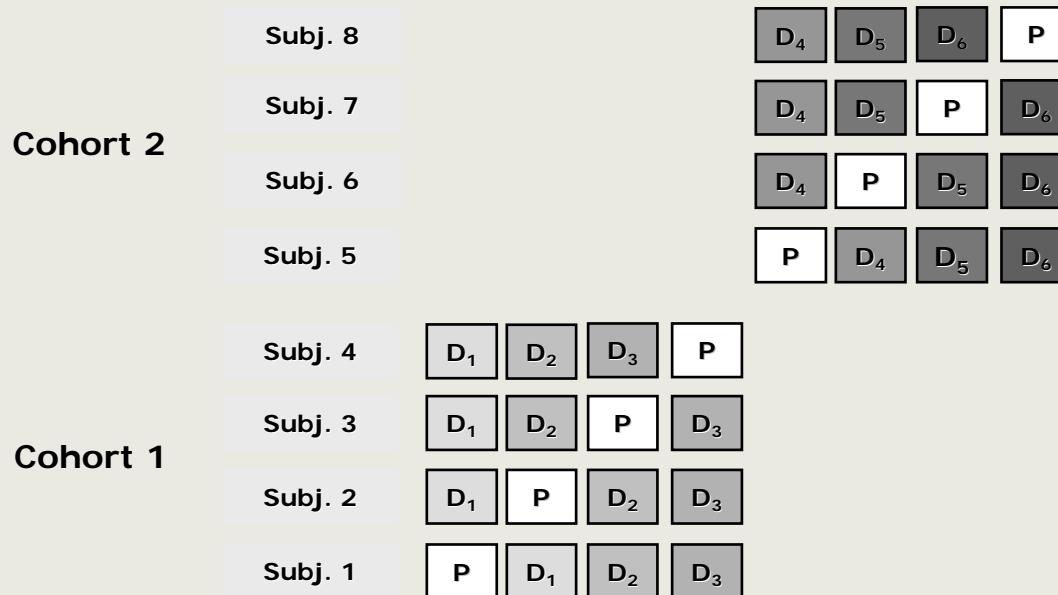
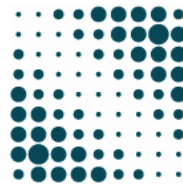
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Parallel Group  
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Single Dose  
6 active + 2 placebo

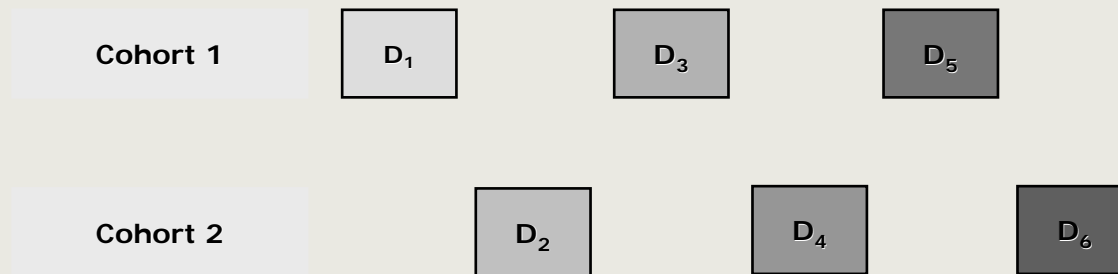


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Thus more information is obtained from fewer subjects and the designs are more efficient in estimating dose proportionality.

To achieve the same precision the alternate designs require fewer subjects than the sequential design

## **Further studies needed regarding**

- Intra- and inter-subject variability assessment

- Statistically based dose increments

- Statistically based safety evaluation

# Cohort Size in Phase I.



## Question:

- Number of subjects per group in Dose Escalation studies in healthy volunteers?

## Present:

- No consensus in study design.
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- Ranges from 2 to 10 treated subjects per dose group.



# Cohort size in Phase 1

## **Detectable event rates in active cohorts**

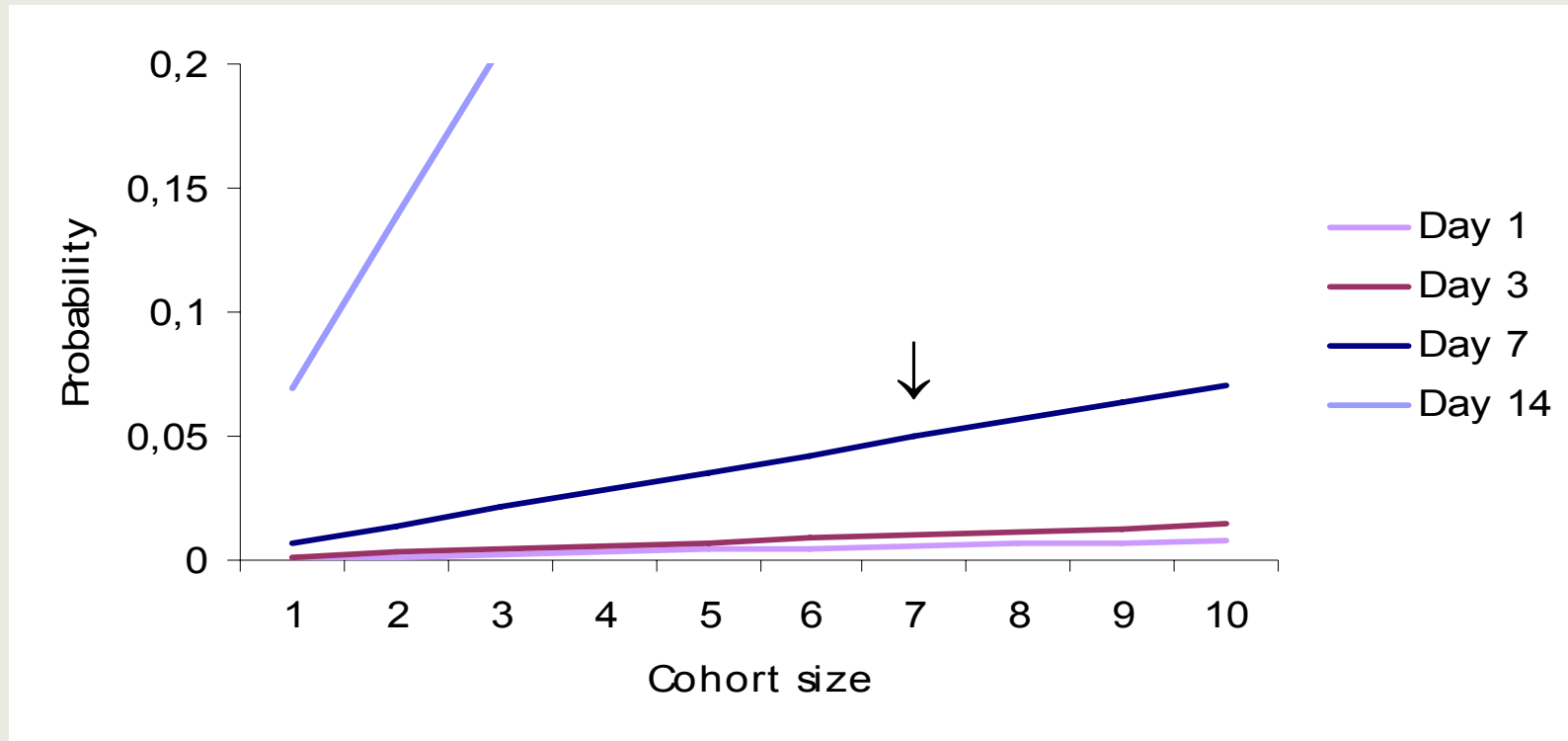
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The risk increases with increasing cohort size. For cohorts with 8 or more active subjects the calculated background rate for safety biomarkers (ALT, AST, AP, and  $\gamma$ GT) the spontaneous event rate exceeds 0.05

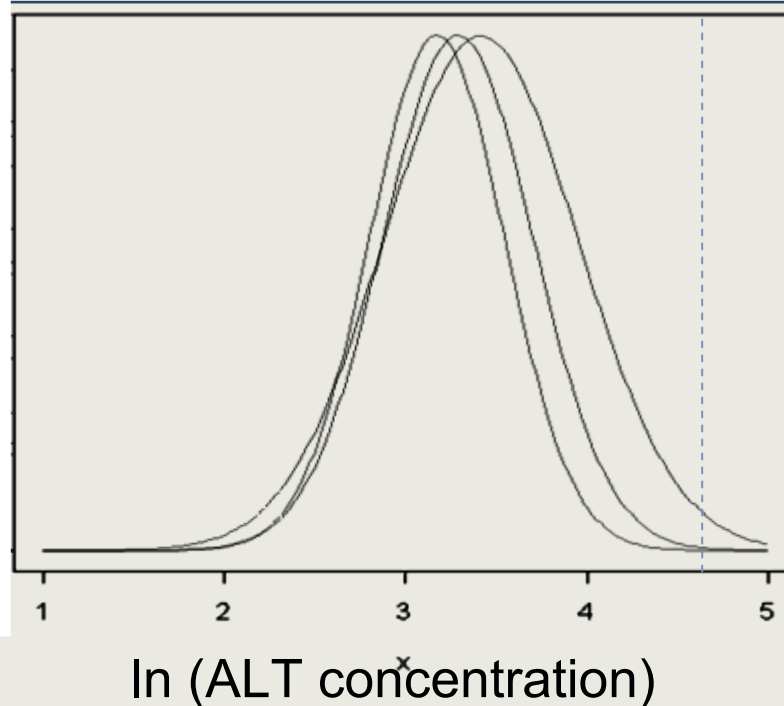
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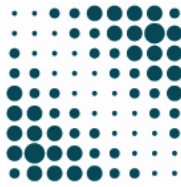
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The calculated probability distributions for ln ALT at day 1, 7 and 14 for placebo subjects in the Multiple Dose studies. The blue line indicates 2x ULN. With increasing hospitalisation period, the risk of an enzyme level above 2xULN is increased.

# Phase I : Cohort sizes



## Conclusions

- There is a time-dependent hospitalisation-induced increase in ALT levels in phase 1 dose escalation studies
- The probability of a spontaneous increase in ALT levels to two times the ULN increases with time and cohort size.
- This background rate aid the determination of cohort size.
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## Phase I: Research Proposal



### *Present procedure:*

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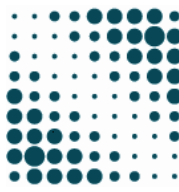




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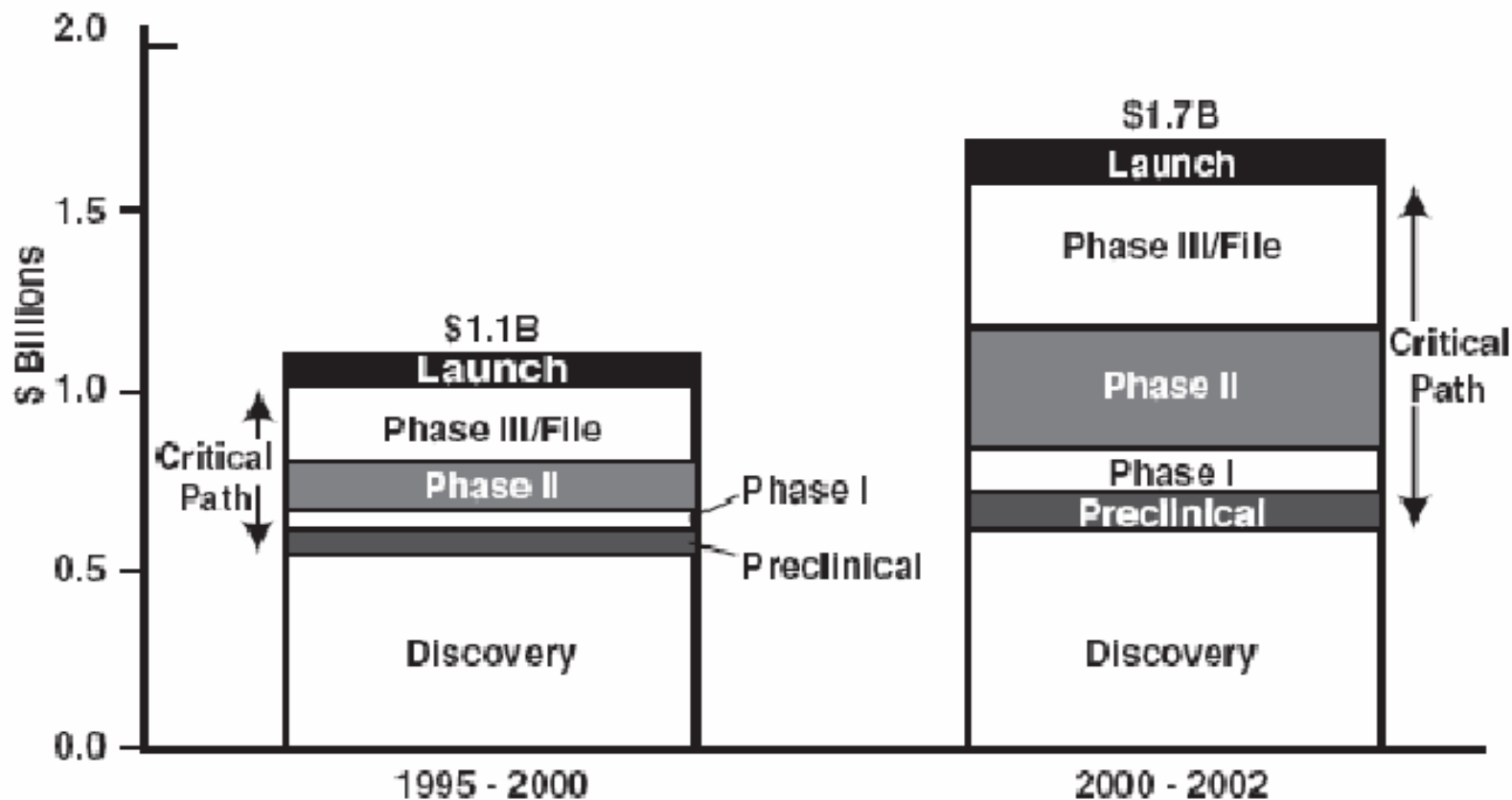
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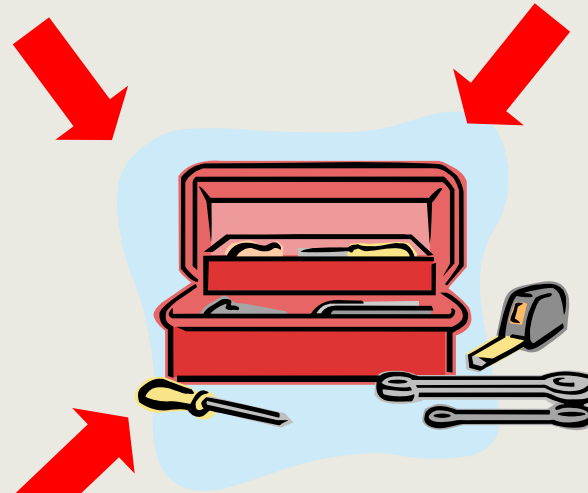
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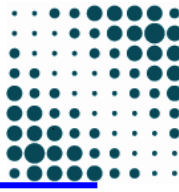
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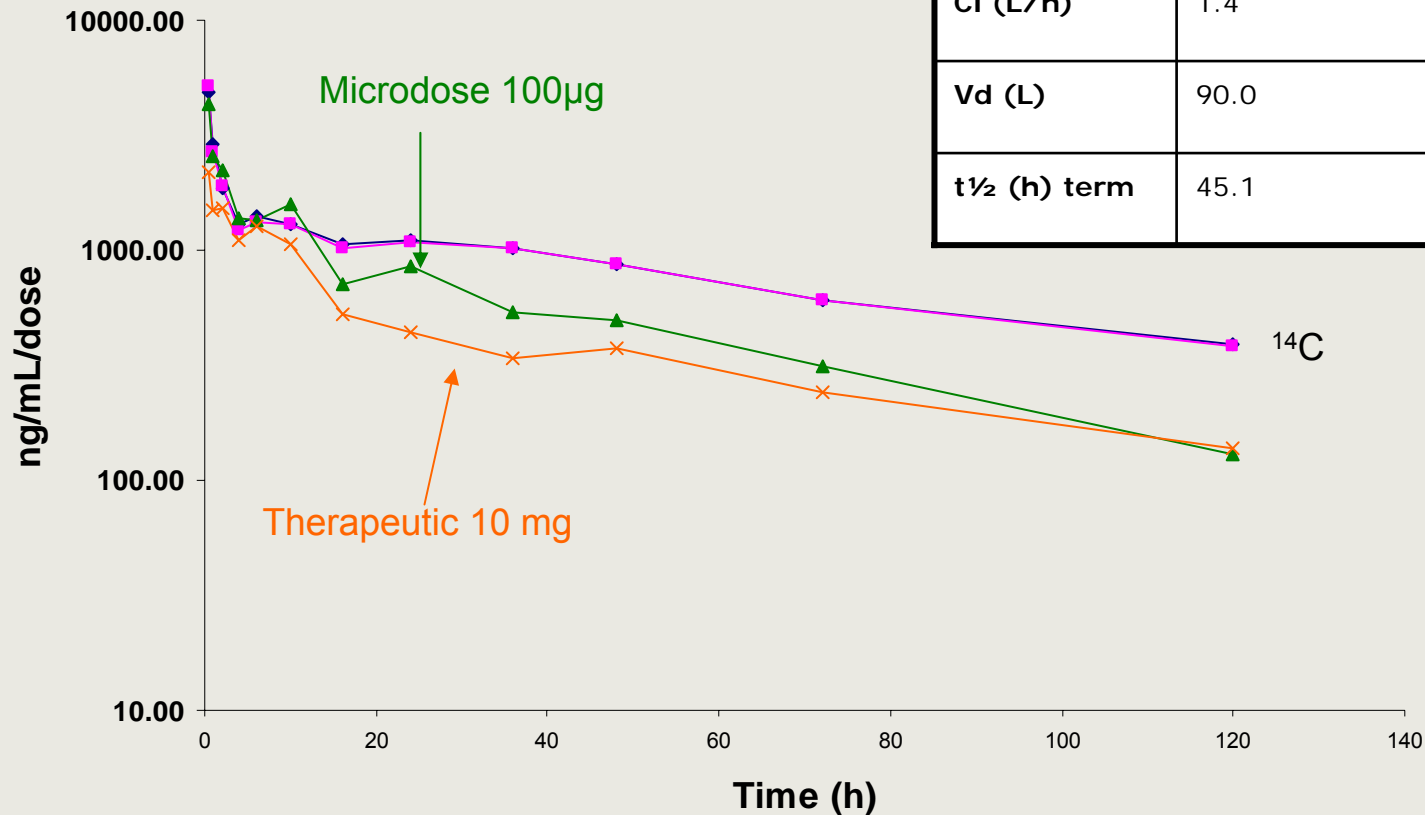


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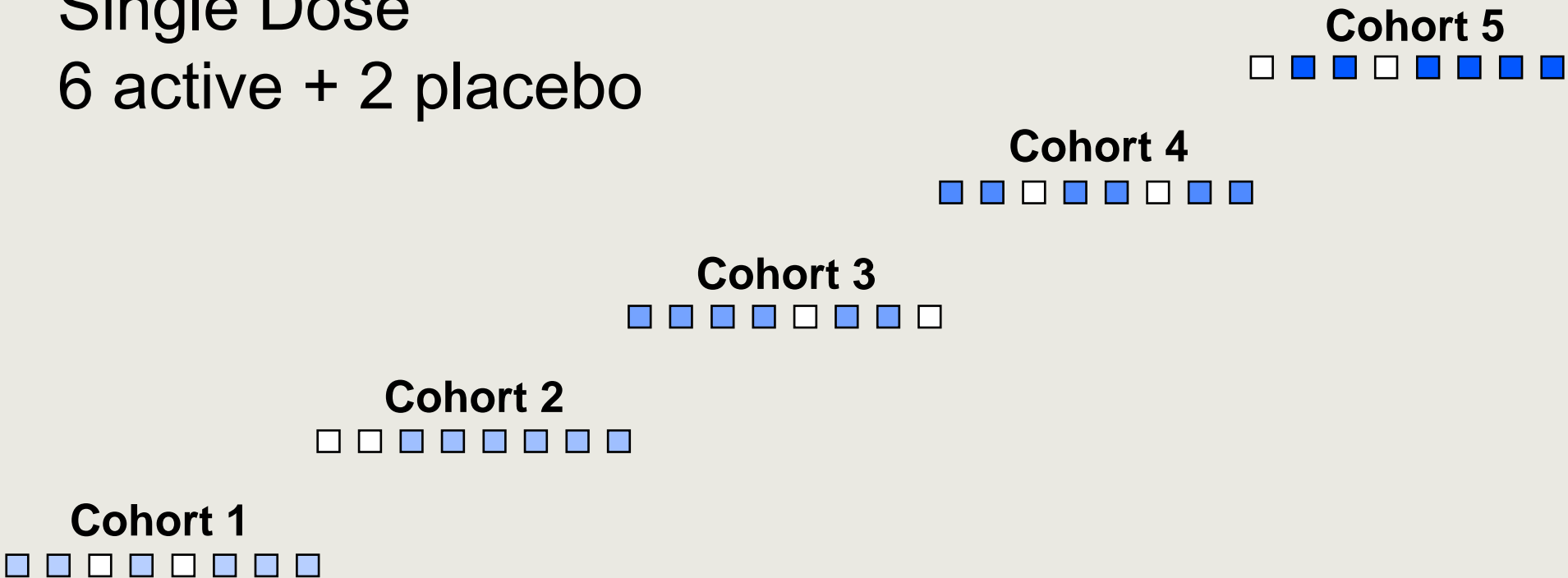
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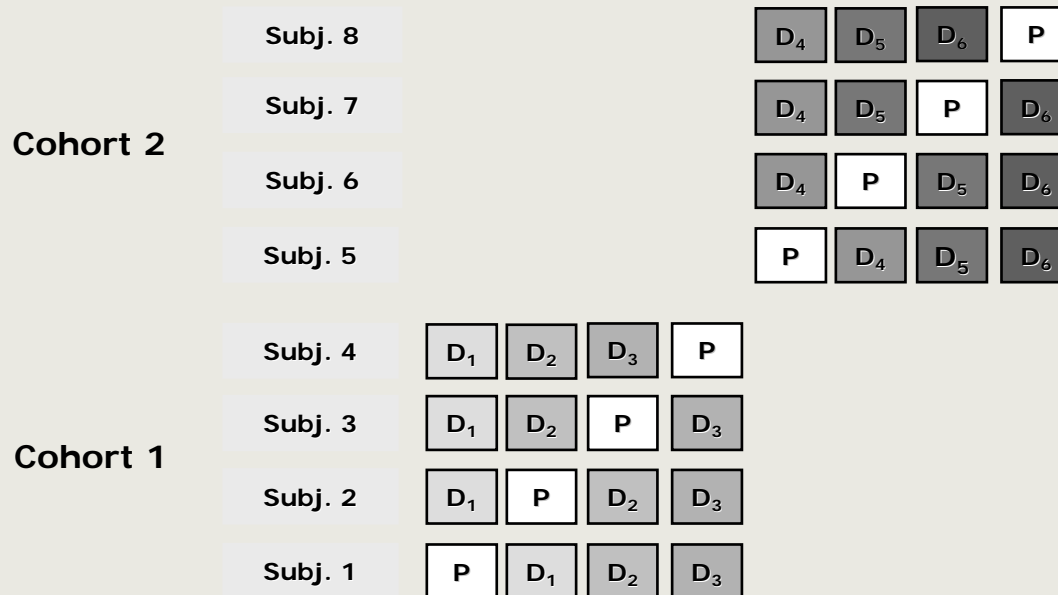
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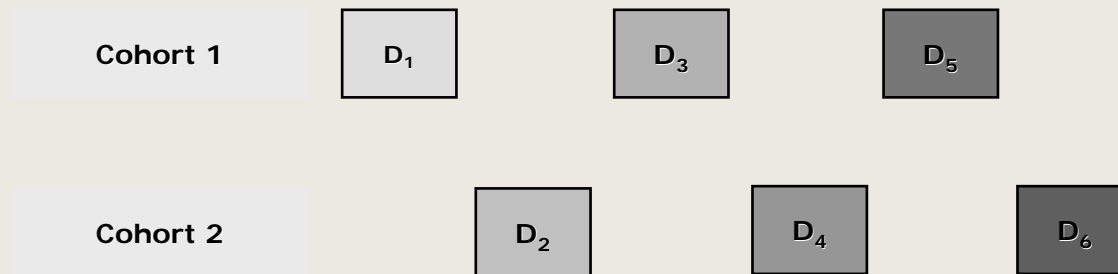


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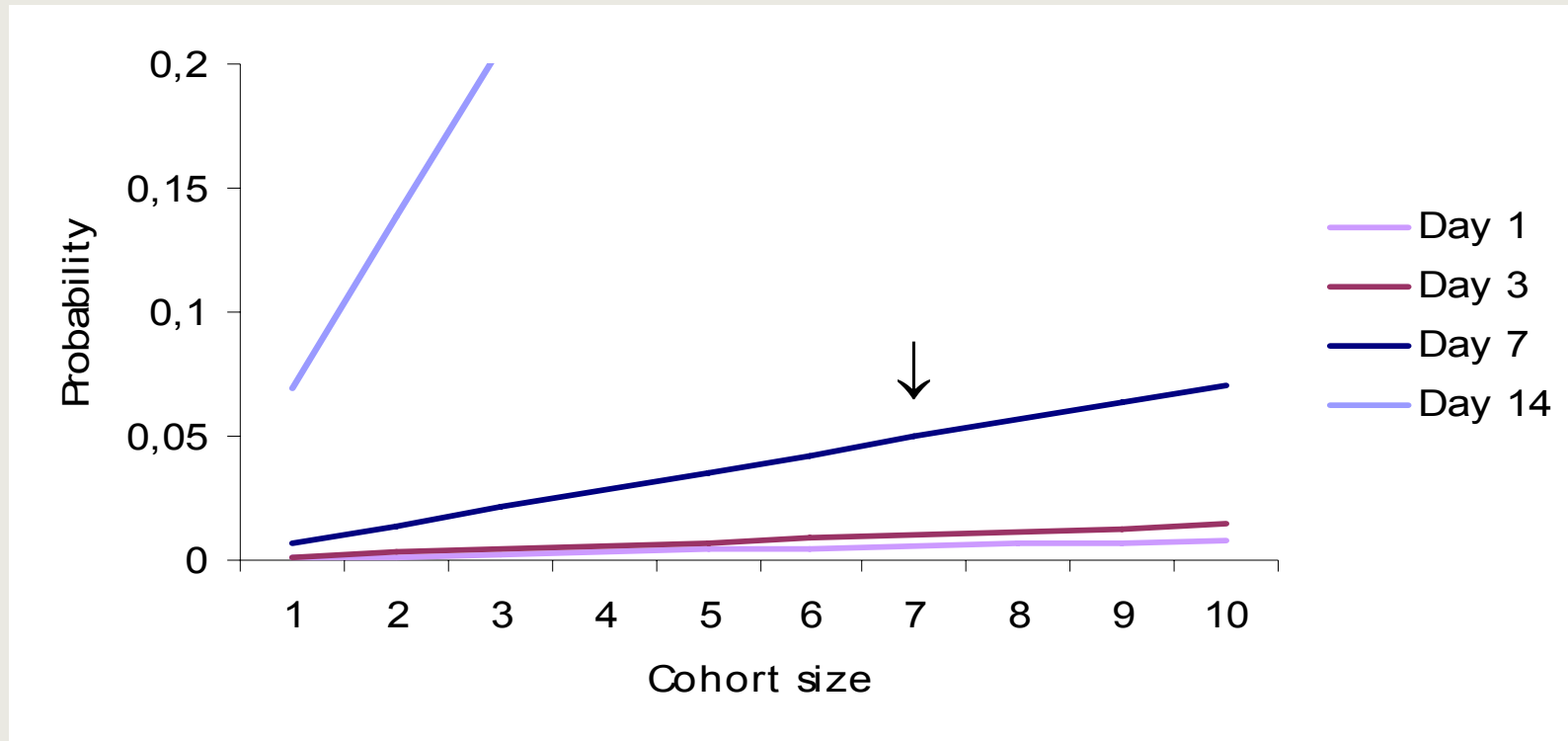
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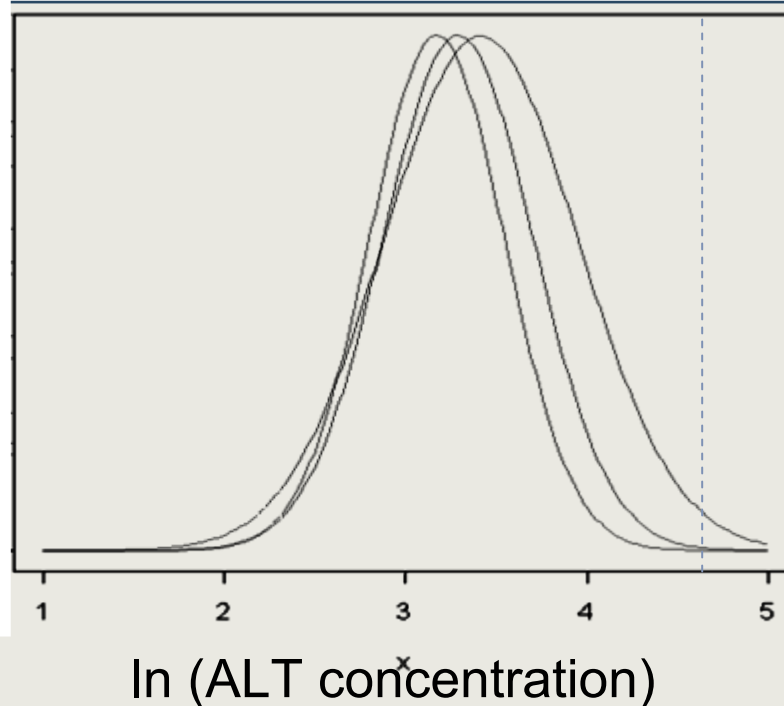
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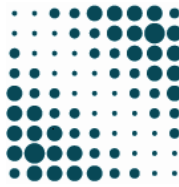
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# Drug Development: A Paradigm Shift is Needed

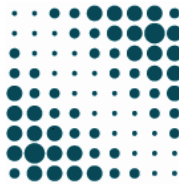


*Rethinking of the drug development  
process*

How to implement all modern  
technological opportunities available in  
the future drug development process?

Through research and validation for  
adoption of regulating authorities.

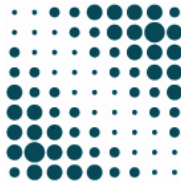
# FDA Statement



*"Often, developers are forced to use the tools of the last century to evaluate this century's advances"*

FDA report March 2004

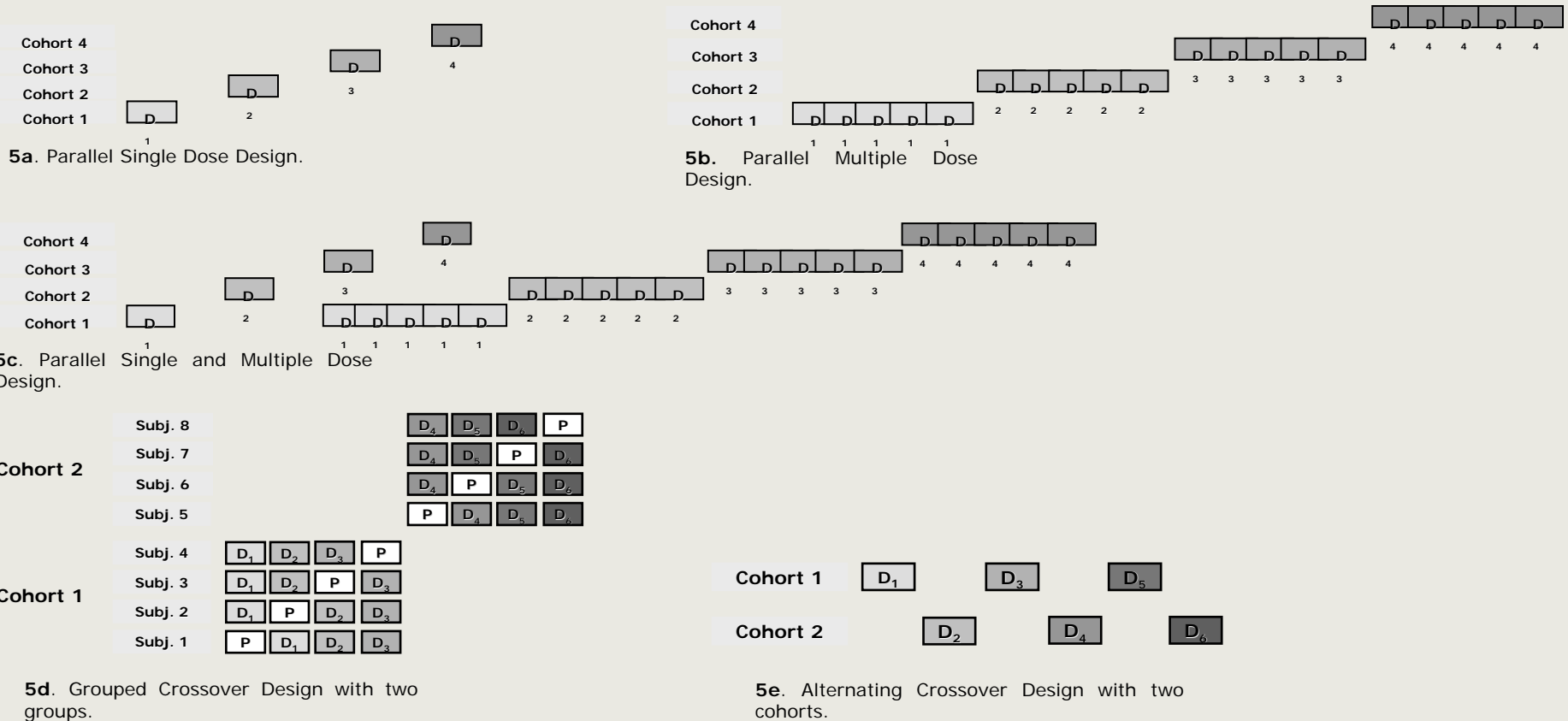
# How to Rethink Drug Development and Approval



- **Obstacles (Real & Perceived)**
  - Very complex process
  - Many stakeholders
  - Conflicting interests, little data sharing
  - Rigid regulations
- **Promoters**
  - Promising new methodologies and technologies
  - Economical pressure from the innovation gap
  - Gain by avoiding the current research duplications and repetition
  - The demand for affordable medicine
- **What is needed**
  - Research, validation, funding (co-financing)
  - Organization, coordination, collaboration
  - Foresight and leadership
  - 10 years time horizon



# Dose escalation designs



Designs: Parallel Single Dose Escalation (a), Parallel Multiple Dose Escalation (b), Parallel Single and Multiple Dose Escalation (c), Grouped Crossover Dose Escalation (d), and Alternating Crossover (e).

# New Safe Medicines Faster Initiative



## Two tracks

- Streamlining by optimising drug discovery and development to remove bottlenecks.
- Fresh Approach by re-evaluating the entire process and create new efficient flow of knowlegde and management based on scientific advances

EUFEPS, March 2000

# Methodological Research for Drug Development



## Need for precompetitive research

- to remove bottlenecks of the process
- to provide evidence and validation
- to support regulatory decisions

# Some Methodological Research Topics



Systems biology  
Biosimulation PK-PD relation  
Modelling and simulation  
Modelbased drug development  
Safety science (preclinical, clinical)  
Biomarkers  
Translational research  
Microdosing  
Clinical trial designs  
Phase 1 improvements (evaluation of immunogenicity)  
    Adaptive trials, learn and confirm trials  
Knowledge management

# Translational Research



The process of applying ideas, insights and discoveries generated through basic scientific inquiry to the treatment or prevention of human disease.

Studies on animal models of disease are translational, provided they are relevant to the human condition and allow us to make specific predictions about diseases in patients.

# Detection techniques



## Accelerator Mass Spectrometry AMS

- A high sensitivity detection system (developed for archaeology samples) measuring atoms separated by differences in mass, charge and energy.
- The  $^{12}\text{C}$ ,  $^{13}\text{C}$  and  $^{14}\text{C}$  atoms are individually counted

P<sub>ositron</sub> E<sub>mission</sub> T<sub>omography</sub>

PET Radiotracers have short half-lives and limited specificity  
Plasma levels can be quantified using on column focusing  
packed capillary LC-Electrospray ionisation MS

# 5MV AMS INSTRUMENT



# Microdosing:



## Further research perspectives

- Back-up primate (monkey) studies at different (higher) dose levels
- Labelling the drug at metabolic stable sites for PK
- Molecular interaction on basis of affinity for target
- Subsequent characterisation of drug in displacement studies.

# Data evaluation in First-in-Man Studies



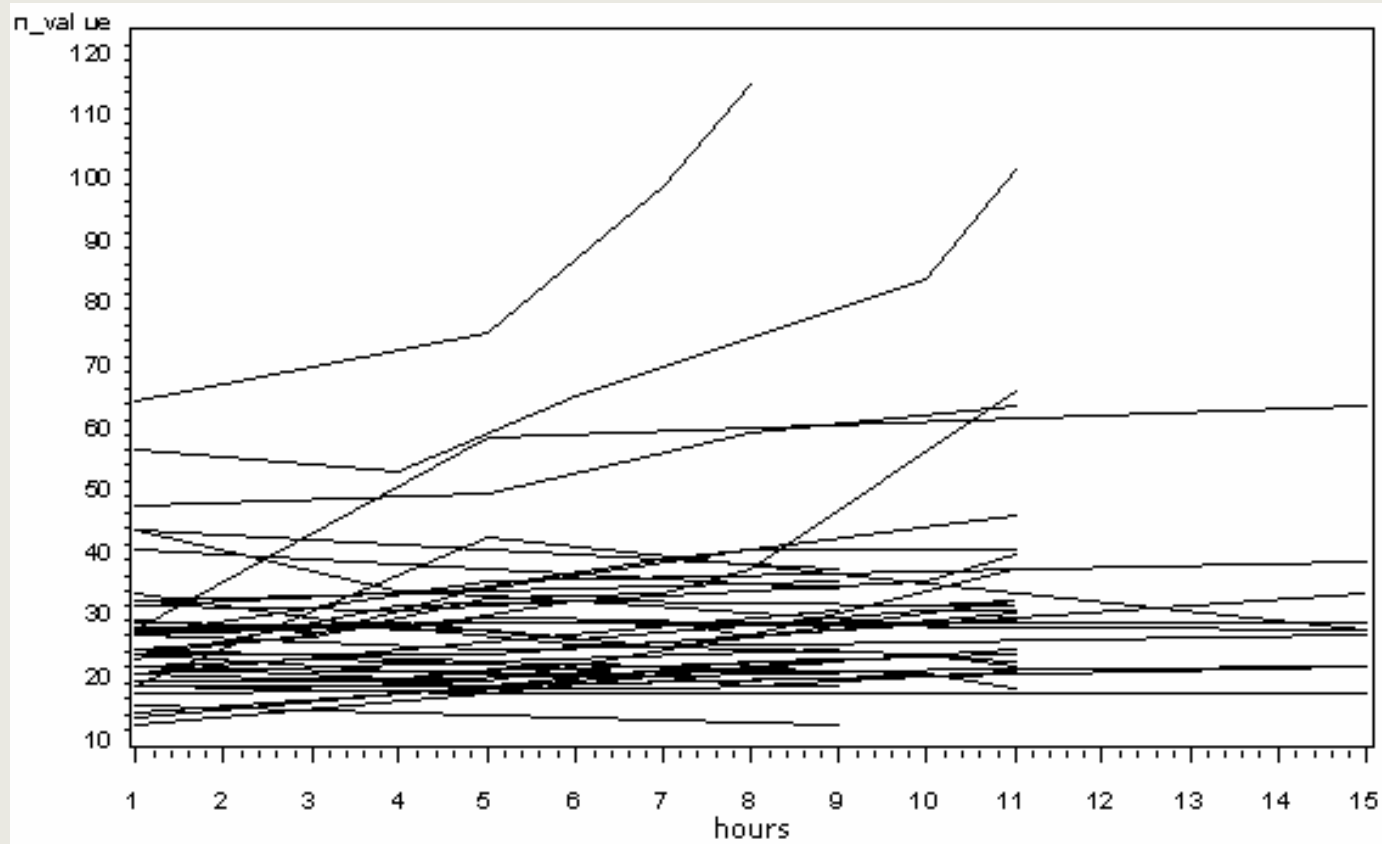
- Thorough data evaluation of First-in-Man studies important
- Analysis of Minimum Safety Data only results in lost information
- Proper data management with designed database is imperative
- More information early - though with poor statistical significance - will result in better and faster development.



## Recommendation:

- The Active Cohort Size in Phase I Dose Escalation studies should be at least 6 subjects.
- The background rate for biomarkers point to max 8 subjects

# Alanine aminotransferase levels during the hospitalisation period



The ALT levels in the 42 placebo subjects analysed from the multiple dose studies. The enzyme changed over the study periods.